## REMARKS

Claims 1-6, as amended, and new claims 7-14 are pending in this application for the Examiner's review and consideration. Claim 1 was amended to recite that $R_6$ is methyl and that $R_8$ is hydrogen or methyl. Support for $R_6$ being methyl and $R_8$ being hydrogen or methyl comes from the examples (*See, e.g.,* Specification, page 35, line 1 to page 60, line 22) and the preferred compounds recited in claim 3, each of which describe a compound wherein $R_6$ is methyl and $R_8$ is hydrogen or methyl. Claims 4-6 were amended to more clearly and distinctly recite the invention. New claim 7 depends from claim 4 and is directed to a preferred embodiment wherein the cancer is carcinoma of the breast, ovary, or colon (*See, e.g.*, Specification, page 8, lines 24-25). New claims 8-13 are similar to claims 4-6 but recite administering to a patient in need of treatment a therapeutically effective amount of a compound of claims 2 and 3, respectively. Each of new claims 7-13 is supported by the specification as filed, and no new matter has been added. New claim 14 recites a preferred embodiment of the compound of claim 1. Furthermore, no fee is due for these amendments since less than twenty claims have been presented in total.

## THE INVENTION

Epothilones are a class of microtubule-stabilizing agents with a taxol-like mechanism of action. [D.M. Bollag, *Exp. Opin. Invest. Drugs* (1997), 6(7): 867-873 ("Bollag")]. Since the introduction of epothilones into the art, many groups have been designing, synthesizing, and testing epothilones. [D. Schinzer et al., *Angew. Chem. Int. Ed. Engl.*, 1997, 36, No. 3, 523-524; K.C. Nicolaou, et al., *J. Amer. Chem. Soc.*, 1997, 119, 7974-7991; K.C. Nicaloau et al., *Angew. Chem. Int. Ed. Engl.*, 1996, 35, No. 20, 2399-2401; A. Balog et al., *Angew. Chem. Int. Ed. Engl.*, 1996, 35, No. 23/24, 2801-2803]. Claims 1-3 of this application are directed to novel epothilone molecules wherein the structure of the 16-member cyclic epothilone ring or substituents attached to the 16-member cyclic epothilone ring are modified. Claims 4-6 are directed to methods of treating cancer, hypoproliferative cellular disease, and treating a disease associated with angiogenesis in a patient which comprises administering to the patient a therapeutically effective amount of a compound of the invention.

**SUBMISSION OF JOURNAL ARTICLES**

The Examiner requested copies of the journal articles listed on the Form PTO-1449. Applicants attach herewith, for the Examiner's convenience, a legible copy of each publication and a revised form PTO-1449. Applicants respectfully request that the Examiner execute this form to indicate consideration of these references.

**THE REJECTION OF CLAIMS 1-6 AS BEING AN IMPROPER MARKUSH GROUP SHOULD BE WITHDRAWN**

The Examiner rejected claims 1-6 as being an improper Markush grouping for the reasons set forth on pages 2-3 of the Office Action. The Examiner alleges that the recited compounds, while possessing a common utility, present a variable core and, thus, the Markush groups represented by the terms W, $Z_1$, and $Z_2$, where W, $Z_1$, and $Z_2$ have variable different definitions, renders the claims improper. Applicants respectfully traverse the rejection.

Applicants respectfully submit that this rejection is improper since the Examiner has not set forth any statutory basis (*e.g.*, under 35 U.S.C. §§ 101 or 112) for rejecting these claims. The proper action for addressing an improper Markush group is a restriction requirement. The claims, however, were not restricted by the Examiner before examination on the merits. Indeed, the Examiner has admitted that the subject matter of the invention is searchable by examining the claims on the merits. To now reject the claims, after a search and examination on the merits, as being drawn to an improper Markush group, is improper.

Furthermore, the Examiner's basis for the rejection is improper. Applicants respectfully submit that the compounds of Formula V are drawn to a proper Markush group. The MPEP states that "it is improper for the Office to refuse to examine that which the applicants regards as their invention unless the subject matter in a claim lacks unity of invention." MPEP 803.02. The MPEP goes on to state that "unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature as being essential to that utility." MPEP 803.02. As acknowledged by the Examiner, the compounds of Formula V share a common utility, *i.e.*, they have utility as cytotoxic or mictotubule-stabilizing agents (*See, e.g.*, Victory et al. *Bioorg. and Med. Chem. Letters*, (1996), 6(7): 893-898 at page 898 and D.M. Bollag *Exp. Opin. Invest. Drugs* (1997), 6(7):867-873, at page 870) which is accepted and recognized in the art as a useful activity for a pharmaceutical. The compounds of Formula V also share a substantial structural feature that is essential to that

utility, *i.e.,* they are in the class of 16-member ring structures known as epothilones. Applicants note that a Markush type claim can even include independent and distinct inventions, as long as they (1) share a common utility and (2) share a substantial structural feature as being essential to that utility. MPEP 803.02. Accordingly, Applicants respectfully submit that the compounds embraced by Formula V, *i.e.*, those recited in claims 1-6, do constitute a proper Markush group.

Applicants further note that the Markush form of claiming allows the use of an artificial group in cases where there are no true generic words that embrace the group. *In re Schecter,* 205 F.2d 185, 189 (CCPA 1953). The Markush grouping was allowed because it was recognized that "where certain substances, which an inventor by experiment has found available for his purpose, fall within a generic group, but there is nothing to establish that all the species of that group have such similar characteristics as to make them available for this purpose, and there is no known subgeneric term which would include only the species found available." *In re Schecter* at 151 (quoting *Ex parte Burke* 21 U.S.P.Q. 399, 400 (1934)). The Markush grouping is proper when the substances grouped have a "community of chemical and physical characteristics" and that "inclusion in the group is not repugnant to scientific classification." *In re Jones,* 74 U.S.P.Q. 149, 151 (CCPA 1947). Such is the situation for the present invention. As discussed above, in the present case the compounds embraced by Formula V do have a "community of chemical and physical characteristics" and "inclusion in the group is not repugnant to scientific classification." The Examiner has not provided any evidence to the contrary. For the above reasons, Applicants respectfully submit that claims 1-6 do define a proper Markush group. Accordingly, Applicants respectfully request that the rejection of these claims be reconsidered and withdrawn.

**THE REJECTION OF CLAIM 4 UNDER 35 U.S.C. §112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN**

Claim 4 was rejected under 35 U.S.C. §112, first paragraph, for lack of enablement for the reasons set forth on page 3 of the Office Action. The Examiner alleges that the treatment of cancer generally is not enabled by the specification. Applicants respectfully traverse the rejection.

Although claim 4 was rejected on the basis that the specification does not provide an enabling disclosure for the general treatment of cancer, the rejection is in essence a rejection for lack of utility since a rejection under the "how to use prong" of 35 U.S.C. §112 incorporates, as a matter of law, the specification disclose a practical utility for the invention. *In re Ziegler,*

992 F.2d 1197, 1200-01 (Fed Cir. 1993) and MPEP 2107 IV. Compliance with 35 U.S.C. §101 and §112, first paragraph, is satisfied if an Applicant has asserted any specific and substantial utility that is credible. MPEP 2107.01. Furthermore, assertions of utility in a specification are presumed to be true and "must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." MPEP 2107.01 (citing *In re Langer*, 503 F.2d 1380, 1391 (CCPA 1974)). To overcome the presumption Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. MPEP 2107.01 III A.

In the present case, Applicants have asserted that the claimed epothilone molecules can be used to treat cancers. Moreover, this utility is clearly credible. One of ordinary skill in the art would readily recognize that epothilone derivatives would have this utility (*See, e.g.*, Bollag et al., *Cancer Research*, 55, 11 2325-33 ("Bollag"), reference CC on Form PTO 1449). Bollag discloses that epothilones A and B are mictrotubule-stabilizing agents having a neoplastic mechanism similar to that of paclitaxel (Taxol®). Clearly, one of ordinary skill in the art would find it credible that the claimed epothilone molecules would have a similar mechanism and could be utilized for the treatment of cancer. Thus, Applicants have complied with 35 U.S.C. §112, first paragraph, by asserting a specific and substantial utility that is credible. MPEP 2107.01.

The Examiner, however, cites *In re Buting*,163, U.S.P.Q., 689 (CCPA 1969) to support the position that the claims are not enabled. Applicants note, however, that the MPEP identifies *In re Buting* as one of a number of old cases that held treating cancer in humans was incredible but then goes on to state that "[t]he fact that there is no known cure for a disease, however, cannot serve as a basis for such a conclusion that an invention lacks utility." MPEP 2107.02 VI.

Applicants respectfully direct the Examiner's attention to *In re Brana*, 34 U.S.P.Q. 2d, 1436 (Fed. Cir. 1995) where the court specifically addressed the rejection now being made. In *In re Brana* claims directed to compounds for use as antitumor substances were rejected by the Examiner under 35 U.S.C. § 112, first paragraph, for failing to disclose a specific disease and the allegation that prior art tests against murine tumor models were not sufficient to establish a reasonable expectation that the claimed compounds had practical utility. The court, however, reversed the rejection and held that the utility requirement of 35 U.S.C. § 112, first

paragraph, was satisfied since the claimed compounds were structurally similar to a compound known to have activity against *in vivo* murine tumor models even though "some laboratory oncologists are skeptical about the predictive value of *in vivo* murine tumor models for human therapy" *Id.* at 1442. Similarly, in the present case, the documented fact that epothilones are mictrotubule-stabilizing agents having a neoplastic mechanism similar to that of paclitaxel (Taxol®) (*See, e.g.*, Bollag) is sufficient to satisfy the utility requirement of 35 U.S.C. § 112, first paragraph. One of ordinary skill in the art would certainly find it credible that the claimed compounds could be utilized for the treatment of cancer. Indeed, the court in *In re Brana* stated that "[t]he purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principals." *Id.* At 1441. For the above reasons, Applicants respectfully submit that they have asserted a specific and substantial utility that is credible and have satisfied the requirements of 35 U.S.C. § 112, first paragraph.

Furthermore, the Examiner has failed to provide any factual basis or documentary evidence upon which it could be established that a person of ordinary skill in the art would not consider the asserted utility as being credible to overcome the presumption of utility. The Examiner cites an article by B. Balasubramian, "Recent Developments in Cancer Cytotoxics," Annual Reports in Medicinal Chemistry, 33, 9, 151, (1998) ("Balasubramian") as stating that the "successful treatment of adult solid tumors remains a formidable challenge." This statement does not provide a factual basis or documentary evidence upon which it could be established that a person of ordinary skill in the art would not consider the asserted utility as being credible much less provide the evidence to overcome the presumption of utility. Balasubramian "[does] not question the usefulness as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of Applicants' compounds," which is the proper test for "challenging a presumptively correct assertion of utility in the disclosure." *In re Brana* at 1441. Indeed, the statement in Balasubramian that "[e]pothilone B exhibits potency similar to paclitaxel in tubulin polymerization and cytoxicity assays" further supports Applicants contention that one or ordinary skill in the art would find it credible that the claimed compounds would have utility for the treatment of cancer.

Importantly, Applicants note that they have not claimed a *cure* for cancer, which might raise the level of scrutiny to that being applied by the Examiner. MPEP 2107, IV, 2. Rather, Applicants have claimed a method for the *treatment* of cancer. The MPEP clearly states that "[t]he fact that there is no known cure for a disease, however, cannot serve as the basis for a

conclusion that such an invention lacks utility" and that "[a]n assertion that a claimed invention is useful in treating a symptom of an incurable disease may be considered credible by a person of ordinary skill in the art on the basis of a fairly modest amount of evidence or support." MPEP 2107, IV, 2. The important point is that "[o]nly those claims for which an asserted utility is not credible should be rejected." MPEP 2107, IV, 2. As noted above, claim 4, directed to a method of treating cancer, is credible. Accordingly, Applicants respectfully submit that they have satisfied the proper test set forth in the MPEP for establishing compliance with 35 U.S.C. §112, first paragraph, and that claim 4 is fully enabled. For the above reasons, Applicants respectfully request that the rejection of claim 4 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

**THE REJECTION OF CLAIM 6 UNDER 35 U.S.C. §112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN**

The Examiner rejected claim 6 under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons set forth on page 4-5 of the Office Action. The Examiner alleges that the term "angiogenesis" is not an art recognizable term, that it is unclear what diseases are mediated by an antiangiogenic effect, and that determining whether a disease responds or does not respond will involve undue experimentation. Applicants respectfully traverse the rejection.

Applicants submit that the term "angiogenesis" is an art recognized term. Applicants enclose herewith a copy of Stedman's Medical Dictionary, 26th ed., Williams and Wilkens, p. 85 (1995) ("Stedman's") that defines the term angiogenesis as meaning "the development of new blood vessels." Similarly, J. Folkman et al., "Angiogenesis," J. Biol. Chem., (1992) 267(16): 10931-10934 ("Folkman") states thast "[a]ngiogenesis is a fundamental process by which new blood vessels are formed" (*See, e.g.*, Folkman, page 10931, column 1). Accordingly, one of ordinary skill in the art would readily recognize that an antiangiogenic effect would be the inhibition of the development of new blood vessels and that the inhibition of angiogenesis would arrest cellular proliferation.

Furthermore, one of ordinary skill in the art would readily recognize what diseases are associated with the increased development of new blood vessels and, therefore, would be mediated by an antiangiogenic effect. The specification recites examples of diseases wherein antiangiogenesis properties of the compounds of the invention would be useful for treating the disease. Such diseases include tumors, certain forms of blindness related to retinal

vascularization, arthritis, multiple sclerosis, restinosis, and psoriasis (*See, e.g.*, Specification, page 9, lines 11-17).

It is well known in the art that angiogenesis plays a role in the pathology of a wide variety of diseases. For example, in Torry et al., "Review: Angiogenesis in the Uterus: Potential Regulation and Relation to Tumor Angiogenesis," Am J. Reproductive Immunology (1992) 27:171-179 ("Torry") it is stated that "[o]nly during certain pathological conditions, such as, arthritis, diabetic retinopathy, muscle hypertrophy, chronic inflammation, wound healing, and solid tumor growth does the body exhibit significant angiogenesis" (*See, e.g.*, Torry, page 271, column 1). Similarly, in Folkman it is stated that "many diseases are driven by persistent unregulated angiogenesis" and goes on to discuss arthritis, diabetic retinopathy, ocular neovascularization, and tumor growth as examples of diseases that are angiogenesis-dependent. Indeed, angiogenesis diseases are a recognized group of diseases and the treatment of angiogenesis is a therapy for all the diseases (*See, e.g.*, Colville-Nash, P.R. et al., "Review: Angiogenesis and Rheumatoid Arthritis: Pathogenic and Therapeutic Implications," Ann. Rheum. Dis. (1992) 51:919-925 ("Colville-Nash") at page 919, column 1). In Colville-Nash it is stated that "[angiogenesis] may be beneficial as in wound healing, but may also contribute to the pathogenesis of some conditions - for example, tumor growth, neovascular glaucoma, and rheumatoid arthritis. Such diverse conditions may be grouped together as 'angiogenesis-dependent diseases,' and modulation of the angiogenic component in their pathogenesis may be used to control progression" (*See, e.g.*, Colville-Nash, page 919, column 1). Angiogenesis is also important for the growth of tumors and antiangiogenesis compounds can be used to inhibit tumor growth and treat cancer (*See, e.g.*, H. Black, "Angiogenesis-Promoting and Blocking-Comes Into Focus" The Scientist, vol. 12, No. 9, April, 1998 ("Black")). Applicants further note that numerous U.S. Patents discuss the use of antiangiogenic compounds to treat a variety of diseases (*See, e.g.*, U.S. Patent Nos. 5,980,887 to Isner; 5,981,484 to Davidson, 5,985,330 to Collin; 5,948,403 to Sone; 5,990,280 to Van Meir et al.; 5,994,292 to Tosato; 5,994,388 to Udugawa and 5,712,291 to D'Amato). Copies of each of the above-discussed references are enclosed herewith for the Examiner's convenience. Contrary to the Examiner's allegations, one of ordinary skill in the art would readily recognize what is an antiangiogenic effect and what diseases can be treated by providing an antiangiogenic effect. Clearly, as shown by the references cited above, the term "angiogenesis" is an art recognized term and that one of ordinary skill in the art would readily recognize what diseases are mediated by an antiangiogenic effect.

The Examiner further alleges that determining whether a disease responds or does not respond involves undue experimentation and without such research one skilled in the art cannot determine the scope of the claim. Applicants respectfully submit that 35 U.S.C. § 112, second paragraph, only requires that Applicants clearly and precisely sets forth the subject matter of the invention. MPEP 2173.03. Applicants have clearly and precisely sets forth the subject matter of the invention, *i.e.*, a method of providing an antiangiogenic effect in a patient. Accordingly, claim 6 is not indefinite. Moreover, determining whether a given disease responds does not require undue experimentation. Applicants respectfully submit that determining whether a disease responds to a specific compound is well within the level of skill in the art and does not involve undue experimentation and potentially inconclusive research, as alleged by the Examiner (*See, e.g.*, cited references). Indeed, *in vitro* and *in vivo* models are known and commonly used to test without undue experimentation. Furthermore, the specification provides *in vitro* methods for determining biological activity of the claimed compounds by determining tubulin polymerization potency and cytotoxicity (*See, e.g.*, Specification, page 33, line 11 to page 34, line 28). Applicants are not required to find FDA approved drugs. Indeed, the MPEP clearly states that Office personnel should not impose upon applicants the unnecessary burden of providing evidence from human clinical trials." MPEP 2107.02 IV. For the above reasons, Applicants respectfully request that the rejection of claim 6, under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

**THE REJECTION UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN**

The Examiner rejected claims 1 and 4-6 under 35 U.S.C. § 102(b) as being anticipated by Balog et al., *Tetrahedron Letters*, Vol. 38, No. 26, 4529-4532 (1997) ("Balog") for the reasons set forth on page 5 of the Office Action. The Examiner alleges that Balog teaches compounds of Formula I where W and X are both O; $R_1$, $R_2$, $R_6$, and $R_7$ are H; $R_3$ and $R_4$ are methyl; $R_8$ is H or methyl, and $Z_1$ and $Z_2$ are $CH_2$. Applicants respectfully traverse the rejection.

Balog discloses the synthesis of an 8-desmethylepothilone A compound. Accordingly, the compound disclosed in Balog and used to reject the claims has $R_6$ being a hydrogen. In contrast, the compounds recited in independent claim 1, as amended, and dependent claims 4-6 require that $R_6$ is a methyl. Thus, the compounds recited in claim 1, as amended, do not encompass the compounds disclosed in Ballog. Since anticipation requires that each and every element of a claim be taught be a single prior art reference, Applicants

respectfully submit that Bollag cannot anticipate the present claims. For the above reasons, Applicants respectfully request that the rejection of claims 1, and 4-6 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

**THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN**

The Examiner rejected claims 1 and 4-6 under 35 U.S.C. §103(a) as being obvious over WO 97/19086 by Höfle et al. ("Höfle") for the reasons set forth on page 6 of the Office Action. Applicants respectfully traverse the rejection.

Höfle relates to the preparation of certain epothilone derivatives that are derivatives of naturally occurring epothilones. The compounds disclosed in Höfle, however, are completely different from the compounds recited in claim 1 of the present application. For example, structure 3 in Höfle requires that $B_1$ and $B_2$ (of applicant's claim 1) are connected, unlike in the compounds of the present invention; structures 4-5 of Höfle include different G groups from those of applicant's claims; structure 6 of Höfle includes a carbon-carbon double bond in the macrolide between carbons 2 and 3, unlike in the compounds of the present invention; and structure 7 of Höfle is not a macrolide at all but an acyclic system. The only remaining structures in Höfle are structures 1 and 2, which are very similar to epothilones A and B. These structures, however, are excluded by the proviso in claim 1. Thus, each of the epothilone derivatives disclosed in Höfle are different from the epothilones recited in the claims of the present application, as amended.

The epothilones recited in claim 1 are novel and distinct, particularly from any taught by Höfle. For example, the compounds of claim 1 include lactams ( X = O and W = $NR_{15}$), cyclic ethers (X = H, H and W = O), and cyclic amines (X = H, H and W = $NR_{15}$) none of which are disclosed or suggested in Höfle. The compounds of claim 1 also include lactones, however, the proviso in claim 1 excludes the lactones disclosed in Höfle. Moreover, there is absolutely no disclosure or suggestion in Höfle to modify the compounds disclosed by Höfle in a manner to arrive at the claimed compounds. Furthermore, Höfle provides no reasonable expectation that the compounds recited in claim 1 would provide a compound having activity. The proper test for obviousness not only requires that there be motivation to modify the reference but also that one skilled in the art would have a reasonable expectation of successfully completing the claimed invention. *See In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Höfle

does not provide one of ordinary skill in the art with the required suggestion, much less a reasonable expectation of success in arriving at the pending claims.

The Examiner, however, alleges that "one of ordinary skill in the art at the time the invention was made would have been motivated to select the next adjacent homolog of the methyl group which is part of the proviso at the end of claim 1 as well as other possibilities from the generically disclosed alternatives of the reference." Applicants respectfully submit, however, that claim 1, as amended, does not include the *next adjacent homolog of the methyl group*. Rather claim 1, as amended, recites that $R_8$, *i.e.*, R in Höfle, must be a hydrogen or methyl.

Applicants further note that even if Höfle did disclose a homolog of the claimed compounds, which Applicants respectfully submit that he does not for the reasons discussed above, that the mere existence of a homolog is, alone, not enough to establish obviousness. For example, the court in *In re Mills*, 281 F.2d 218, 224 (CCPA 1960) (citing *In re Hass*, 141 F.2d 127, 129) held that "whether an invention exists over prior art isomers and homologs is a question to be decided in each case." The court went on to state that "[h]omology per se should, therefore, be treated as a chemist would treat it, being nothing more than a fact which must be considered with all other facts before arriving at the conclusion of 'obviousness.'" Thus, the mere existence of homologs is not enough to establish obviousness (*See also*, MPEP 2144.09).

Indeed, the court in *In re Langer,* 465 F.2d 896 (CCPA 1972) stated that "the presence in the reference of an isolated hindered amine falling outside the scope of the appellants' claims does not, by itself, apprise the ordinary artisan of the significance of hindered amines as a class." *Id.* At 899. Similarly, the mere disclosure in Höfle of an epothilone that is a lactone falling outside the scope of the compounds recited in independent claim 1 cannot, by itself, render the compounds recited in claim 1 obvious. Höfle cannot apprise the ordinary artisan of the significance of modifying the structure of the 16-member cyclic epothilone ring or substituents attached to the 16-member epothilone ring when there is no suggestion, much less a reasonable expectation of success, that the claimed compounds will have activity. Accordingly, Applicants respectfully submit that Höfle does not render the claims 1 and 4-6 obvious. For the above reasons, Applicants respectfully request that the rejection of claims 1 and 4-6 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

## CONCLUSION

Applicants believes the application is in condition for allowance and earnestly requests reconsideration of the claims and allowance thereof. If the Examiner has any questions or suggestions to expedite allowance of this application, however, the Examiner is respectfully invited to call the undersigned to discuss the matter further.

No amendment fee is believed to be due for this submission. Should any fees be due, however, please charge the fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: June 14, 2001

for Anthony M. Insogna 35,203
Anthony M. Insogna (Reg. No.)

**PENNIE & EDMONDS LLP**
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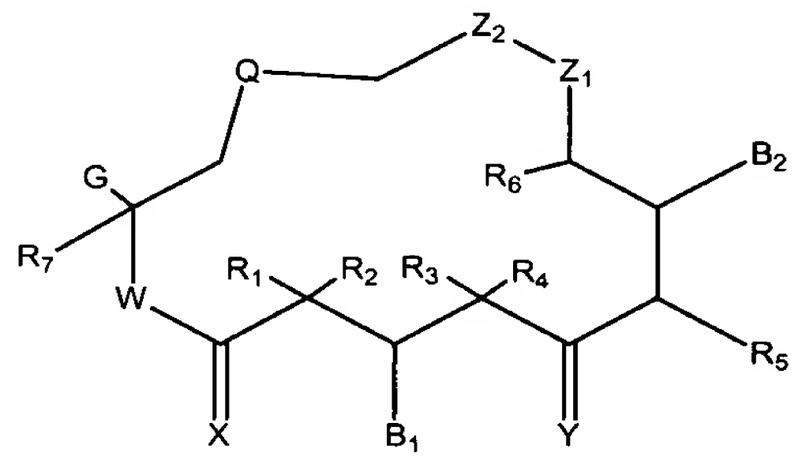
Appendix A

Changes to the Claims

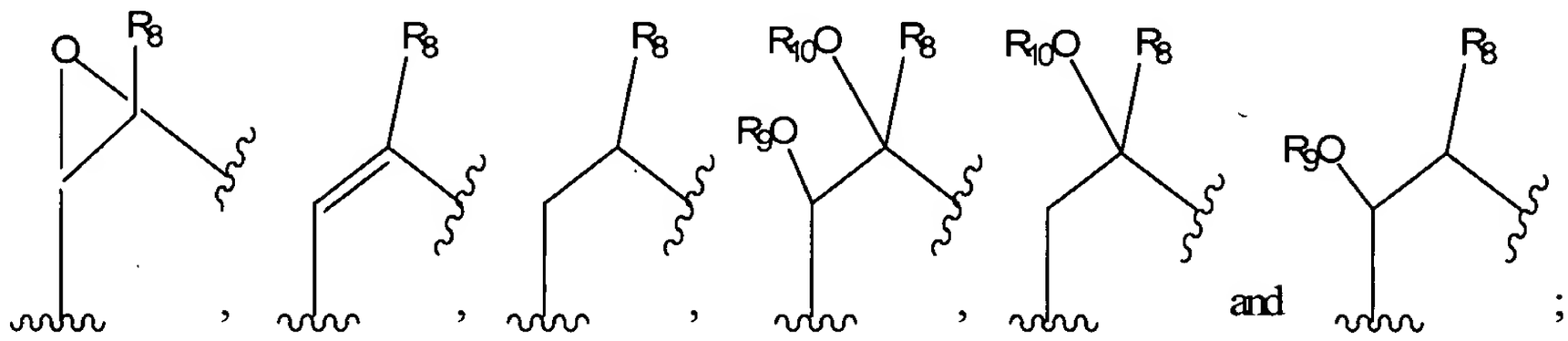
1. (Twice amended) A compound of the formula



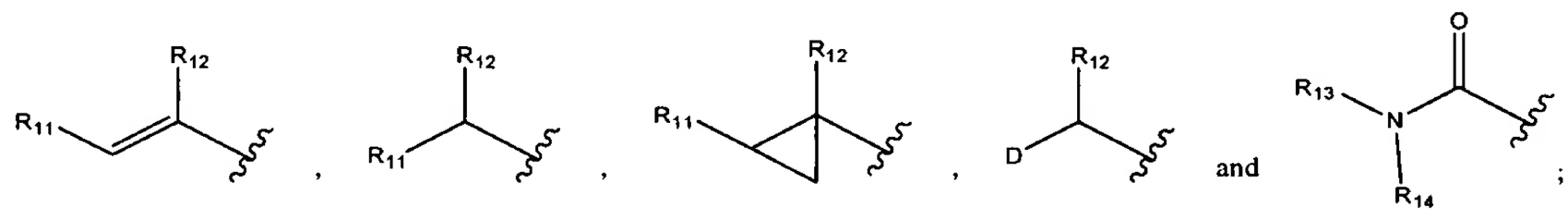

V

wherein

Q is selected from the group consisting of




G is selected from the group consisting of alkyl, substituted alkyl, substituted aryl, heterocyclo,




W is O or N $R_{15}$;

X is O or H, H;

Y is selected from the group consisting of O; H, $OR_{16}$; $OR_{17}$, $OR_{17}$; $NOR_{18}$; H, $NOR_{19}$; H, $NR_{20}R_{21}$; H, H; and $CHR_{22}$; wherein $OR_{17}$, $OR_{17}$ can be a cyclic ketal;

$Z_1$ and $Z_2$ are independently selected from the group consisting of $CH_2$, O, $NR_{23}$, S, and $SO_2$, wherein only one of $Z_1$ and $Z_2$ can be heteroatom;

$B_1$ and $B_2$ are independently selected from the group consisting of $OR_{24}$, $OCOR_{25}$, and O-C(=O)-$NR_{26}R_{27}$, and when $B_1$ is H and Y is OH, H, they can form a six-membered ring ketal or acetal;

D is selected from the group consisting of $NR_{28}R_{29}$, $NR_{30}COR_{31}$ and saturated heterocycle;

$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, [$R_6$,] $R_7$, $R_{13}$, $R_{14}$, $R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{26}$ and $R_{27}$ are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when $R_1$ and $R_2$ are alkyl can be joined to form a cycloalkyl, and when $R_3$ and $R_4$ are alkyl can be joined to form a cycloalkyl;

$R_6$ is methyl;

$R_9$, $R_{10}$, $R_{16}$, $R_{17}$, $R_{24}$, $R_{25}$ and $R_{31}$ are selected from the group consisting of H, alkyl, and substituted alkyl;

[$R_8$,] $R_{11}$, $R_{12}$, $R_{28}$, $R_{30}$, $R_{32}$, and $R_{33}$ are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo;

$R_8$ is hydrogen or methyl;

$R_{15}$, $R_{23}$ and $R_{29}$ are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, $R_{32}C=O$, $R_{33}SO_2$, hydroxy, O-alkyl or O-substituted alkyl; and

the pharmaceutically acceptable salts thereof and any hydrates, solvates or geometric, optical and steroisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

$R_1$, $R_2$ and $R_7$ are H; and

$R_3$, $R_4$ and $R_6$ are methyl; and

$R_8$ is H or methyl; and

$Z_1$ and $Z_2$ are $CH_2$; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

Q is as defined above

are excluded.

4. (Twice amended) A method of treating cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically [providing an] effective amount of a compound of claim 1.

5. (Twice amended) A method of hyperproliferative cellular disease in a patient in need of said treatment which comprises administering to said patient a therapeutically [providing an] effective amount of a compound of claim 1.

6. (Twice amended) A method of providing an antiangiogenic effect in a patient in need of said treatment which comprises administering to said patient a therapeutically [providing an] effective amount of a compound of claim 1 [to said a patient] .